ENVIRONMENTALLY FRIENDLY SYNTHESIS OF NANOSILICA FROM COCONUT COIR ASH AND ITS APPICATION AS A DOXORUBICIN DELIVERY

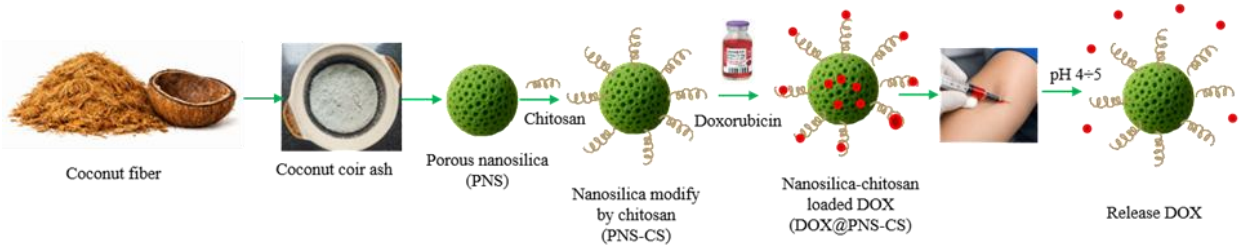
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Abstract. Utilizing agricultural waste to create new, high-value materials is a contemporary research trend pursued by scientists. Coconut coir ash is a waste product from the combustion of coconut coir biochar in boilers. Due to its high silicon content, coconut coir ash is often used as fertilizer. Utilizing coconut coir ash to create nano silica, a high-value material with wide applications in many fields, is a promising approach. In this study, porous nano silica prepared from coconut coir ash will be modified with chitosan, a biopolymer derived from the shells of crustaceans such as shrimp and crabs. This modification with chitosan aims to enhance the transport efficiency of Doxorubicin, a common drug used in the treatment of various cancers. The structure, morphology, particle size, and surface area of porous nano silica were analyzed using modern physicochemical methods, including Fourier transform infrared spectroscopy (FTIR), X-ray diffraction (XRD), scanning electron microscopy (SEM), and BET isothermal analysis. The results showed that the particles were relatively spherical, with an average diameter of approximately 33.9 ± 0.3 nm and a surface area of approximately 322.330 m^2/g. The drug loading efficiency and release characteristics of the material were determined by UV-VIS absorption spectroscopy. The results of the half-maximal inhibitory concentration test (IC50), along with a high drug loading efficiency of 71.75 ± 1.89%, minimum drug release at pH 7.4, and high drug release at pH 4.5, demonstrate significant potential in cancer treatment.

Keywords. Porous nanosilica (PNS), coconut coir, chitosan (CS), Doxorubicin (DOX), half-maximal inhibitory concentration (IC50).



1 INTRODUCTION

Doxorubicin (DOX), an anthracycline-based chemotherapeutic agent, is extensively employed in the treatment of a wide range of malignancies, including breast, bladder, and gastric cancers, as well as soft tissue and bone sarcomas. Following intravenous administration, DOX is distributed throughout the systemic circulation, resulting in exposure of both cancerous and healthy tissues. This non-specific biodistribution limits drug accumulation at tumor sites, thereby compromising therapeutic efficacy while inducing severe adverse effects such as myelosuppression, nausea, and alopecia. These dose-limiting toxicities significantly impair patients' quality of life and may adversely affect treatment outcomes. Consequently, considerable research efforts have been directed toward the development of smart drug delivery systems capable of improving tumor-specific drug accumulation while minimizing systemic toxicity.

Among the various nanocarrier platforms investigated, porous nanosilica (PNS) have attracted considerable attention owing to their favorable physicochemical properties, including excellent biocompatibility, biodegradability, large specific surface area, tunable pore structure, and high chemical stability. These characteristics facilitate high drug-loading capacity, controlled and stimuli-responsive drug release, and

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improved solubility of poorly water-soluble therapeutic agents [1]. Furthermore, the abundance of surface silanol (Si–OH) groups provides versatile sites for chemical functionalization, allowing further enhancement of drug encapsulation efficiency and targeted delivery performance [2, 3].

Conventional synthesis of mesoporous silica nanoparticles commonly relies on tetraethyl orthosilicate (TEOS) as the silica precursor via the sol–gel process. However, safety data provided by major chemical suppliers, including Sigma-Aldrich, Thermo Fisher Scientific classify TEOS as a volatile and flammable compound that poses potential health risks, including skin and eye irritation as well as adverse effects on the respiratory system, liver, and kidneys following prolonged exposure. These concerns have stimulated increasing interest in identifying sustainable and environmentally benign silica sources. Agricultural biomass-derived silica has emerged as a promising alternative, particularly coconut coir, which contains a relatively high silica content and is abundantly available as an agricultural byproduct. The utilization of coconut coir as a silica precursor therefore represents a sustainable strategy to produce porous nano silicas while reducing dependence on hazardous synthetic chemicals.

Despite their high drug-loading capacity and controllable release behavior, mesoporous silica nanoparticles are susceptible to premature drug leakage during systemic circulation, which may reduce therapeutic efficiency. Surface functionalization with chitosan has been proposed as an effective strategy to overcome this limitation. As a naturally derived, biocompatible, and biodegradable polysaccharide, chitosan can improve drug encapsulation efficiency, reduce premature drug release, and enhance the targeting capability of nanocarriers, thereby improving the overall performance of the drug delivery system [4].

Chitosan is produced through the deacetylation of chitin, a naturally occurring polysaccharide abundantly found in the exoskeletons of crustaceans, such as shrimp and crabs, as well as in the cuticles of insects. To covalently immobilize chitosan onto the surface of porous nano silica (PNS), 3-glycidoxypropyltrimethoxysilane (GPTMS) is commonly employed as a silane coupling agent that forms a molecular bridge between the inorganic silica framework and the organic polymer [5]. As illustrated in Figure 1, GPTMS first reacts with the silanol groups on the PNS surface, after which the remaining epoxide group undergoes ring-opening reaction with the amino groups of chitosan, resulting in the successful grafting of chitosan onto the nano silica surface.

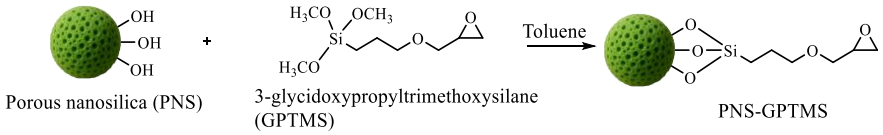


Figure 1: Reaction between porous nano silica and 3-glycidoxypropyltrimethoxysilane (GPTMS)

Following the formation of the GPTMS linker, chitosan was grafted onto the porous nano silica (PNS) surface through an epoxide ring-opening reaction between the amino groups of chitosan and the epoxy groups of PNS-GPTMS under mild acidic conditions. This grafting process resulted in the successful immobilization of chitosan on the PNS surface, as illustrated in Figure 2.

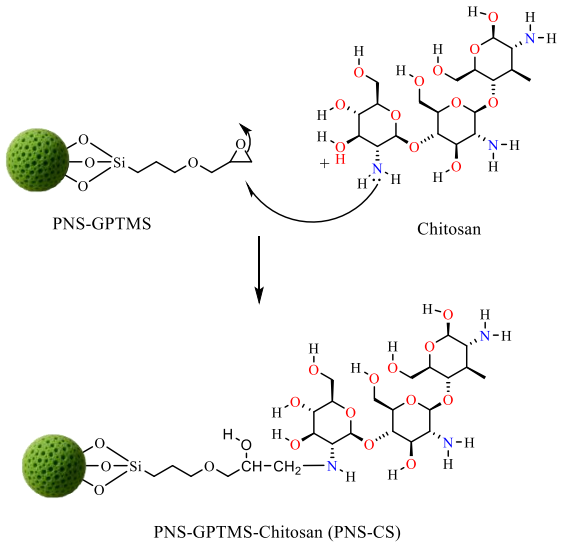


Figure 2: Reaction between PNS-GPTMS and chitosan

Following the surface functionalization of porous nanosilica with GPTMS and chitosan to form the PNS-GPTMS-Chitosan system, abundant amino ($–NH_2$) groups were introduced onto the carrier surface. These amino groups can readily react with the carbonyl group of doxorubicin (DOX) to form imine (Schiff base) bonds. Imine linkages exhibit pH-dependent stability, remaining relatively stable under physiological conditions (pH ≈ 7.4) while undergoing hydrolysis in acidic environments. This acid-labile behavior enables the covalently bound DOX to remain associated with the carrier during blood circulation, thereby reducing premature drug release, but to be released more readily under acidic conditions (pH 4.5–5.5), which mimic the tumor microenvironment and intracellular endosomal/lysosomal compartments. Consequently, the introduction of chitosan is expected to enhance the drug-loading capacity by providing additional reactive amino groups and to impart pH-responsive drug release characteristics to the nanocarrier. Such a pH-sensitive delivery system may improve the selective accumulation and controlled release of DOX at tumor sites while minimizing drug leakage under physiological conditions, thereby enhancing the therapeutic efficacy of targeted cancer treatment.

2 EXPERIMENTS

2.1 Materials

Hydrochloric acid (HCl, 37%, China), sodium hydroxide (NaOH, ≥96%, Xilong), ethanol (≥99.9%, China) and doxorubicin (DOX, 99% from Sigma-Aldrich). Coconut coir originates from coconuts in Ben Tre.

2.2 Synthesis of nanosilica from coconut coir

The coconut coir was washed with water, then naturally dried and heat-treated in a furnace at 500°C for 10 hours. After the heat treatment, gray-white ash was obtained. Next, 3 g of coconut coir ash was dissolved in a 3 N NaOH solution and stirred using a magnetic stirrer at 100°C for 2 hours. The resulting mixture was filtered through filter paper to obtain a clear yellow sodium silicate solution.

The sodium silicate solution was then neutralized with a 2.5 N HCl solution while being stirred with a magnetic stirrer. During the neutralization process, the pH of the solution was adjusted to the range of 6.5–7 until a precipitate appeared, after which the stirring was stopped. The neutralized mixture was transferred into a capped centrifuge tube and centrifuged at 4400 rpm for 18 minutes to separate the solid phase. The solid was then washed three times with distilled water (5 mL each time) and twice with ethanol (5 mL each time). After filtration and washing, the solid was deep-frozen for 12 hours and freeze-dried for 20 hours to obtain the nano silica product. The synthesis process of nano silica from coconut coir was illustrated in Figure 3.

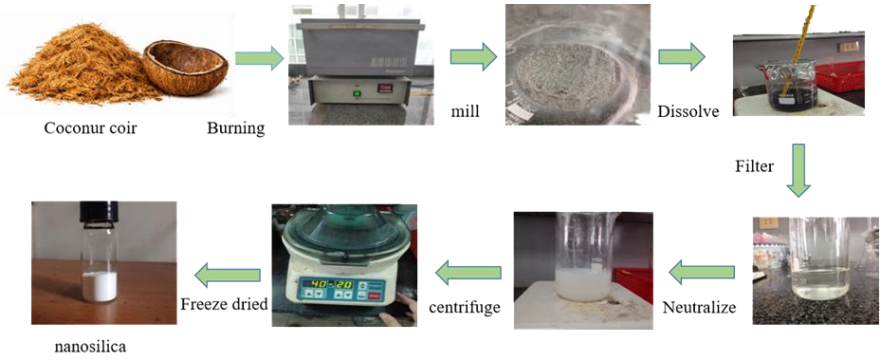


Figure 3: The synthesis process of porous nanosilica from coconut coir

2.3 Modification of nanosilica with chitosan

- **Prepare porous nanosilica link with 3-glycidoxypropyltrimethoxysilane (PNS-GPTMS)**

3-Glycidoxypropyltrimethoxysilane (GPTMS) served as a coupling agent to establish a covalent linkage between the inorganic porous nano silica (PNS) and the organic chitosan matrix. The functionalization of PNS with GPTMS, as illustrated in Figure 1, was carried out as follows.

First, 1 g of PNS-CTAB was dispersed in 30 mL of toluene and sonicated for 1 hour. The suspension was then stirred for 30 minutes at room temperature under a nitrogen atmosphere. Subsequently, 1 mL of 3-glycidoxypropyltrimethoxysilane (GPTMS) was added dropwise to the suspension, and the reaction mixture was continuously stirred for 12 hours at room temperature under a nitrogen atmosphere.

After the reaction, the resulting product was purified by dialysis using a cellulose membrane (molecular weight cut-off: 6000–8000 Da) against 250 mL of a 2 M acetic acid/ethanol mixture (1:1, v/v). The dialysis medium was replaced five times to ensure the complete removal of unreacted reagents and impurities. Finally, the purified product was freeze-dried to obtain PNS-GPTMS as a fine powder.

- **Modification of porous nanosilica by chitosan (PNS-CS)**

The grafting of chitosan (CS) onto PNS-GPTMS was carried out according to the reaction scheme shown in Figure 2.

First, PNS-GPTMS was dispersed in 15 mL of distilled water, then sonicated for 30 minutes. The pH of the suspension was then adjusted to 3.5. Separately, CS was dissolved in 20 mL of distilled water, and the pH of the solution was adjusted to 3.5 before stirring for approximately 30 minutes to obtain a homogeneous solution.

The CS solution was then added dropwise to the PNS-GPTMS suspension. The reaction mixture was stirred at room temperature for 36 hours to allow the grafting reaction to proceed. After the reaction was completed, the product was collected by centrifugation and washed three times with distilled water to remove unreacted reagents and impurities. Finally, the purified product was freeze-dried to obtain the PNS-GPTMS-CS.

2.4 PNS-CS loading doxorubicin (DOX@PNS-CS)

The PNS-CS loading DOX was presented in Figure 4. First, 60 mg of PNS-CS was dispersed in 10 mL of distilled water and sonicated for 30 minutes to obtain a homogeneous suspension. Separately, 15 mg of doxorubicin (DOX) was dissolved in 2 mL of distilled water, and the solution was magnetically stirred for 30 minutes until complete dissolution. The DOX solution was then added dropwise to the PNS-CS suspension, and the resulting mixture was magnetically stirred at room temperature for 24 hours to facilitate drug loading. After the loading process, a 2 mL aliquot was collected to determine the initial DOX concentration.

The remaining suspension was divided equally into three dialysis bags (molecular weight cut-off: 3000–5000 Da), with each bag containing 2 mL of the sample. The dialysis bags were immersed in distilled water and continuously stirred to remove unencapsulated DOX, as illustrated in Figure 4. During the first 6 hours of dialysis, dialysate samples were collected every hour for the determination of the free DOX concentration. At each sampling point, 18 mL of the dialysis medium was withdrawn and immediately replaced with an equal volume of fresh distilled water to maintain sink conditions. Dialysis continued under the same

conditions for an additional 12 hours. The collected dialysate samples were analyzed to quantify the amount of unloaded (free) DOX and to determine the drug-loading efficiency.

The drug loading efficiency (DLE) and drug loading capacity (DLC) of the carrier were calculated according to the following equation:

$$\text{DLE (\%)} = \frac{\text{weight of loaded drug}}{\text{weight of drug used in formulation}} \text{ x } 100\%$$

$$\text{DLC (\%)} = \frac{\text{weight of encapsulated drug}}{\text{total weight}} \text{x } 100\%$$



Figure 4: PNS-CS loads doxorubicin and removes free drug.

2.5 In vitro study of Doxorubicin Drug Release

The in vitro release behavior of doxorubicin (DOX) from the PNS-CS carrier was evaluated using the dialysis method, as illustrated in Figure 5. Each dialysis bag contained 2 mL of the DOX-loaded PNS-CS suspension (DOX@PNS-CS) and was immersed in 18 mL of either phosphate-buffered saline (PBS, pH 7.4) or acetate buffer (pH 4.5). The release medium was continuously stirred throughout the experiment.

Samples of the release medium were collected at predetermined time intervals of 1, 2, 3, 6, 12, 24, 36, 48, 72, 84, and 96 hours over a total release period of 4 days. The concentration of DOX released into the medium was determined using UV–VIS spectrophotometry. All measurements were performed in triplicate, and the results were expressed as the mean values to ensure the reliability of the data.

PBS buffer (pH 7.4) was used to simulate the physiological environment of healthy tissues, whereas acetate buffer (pH 4.5) was employed to mimic the acidic microenvironment of cancer cells.

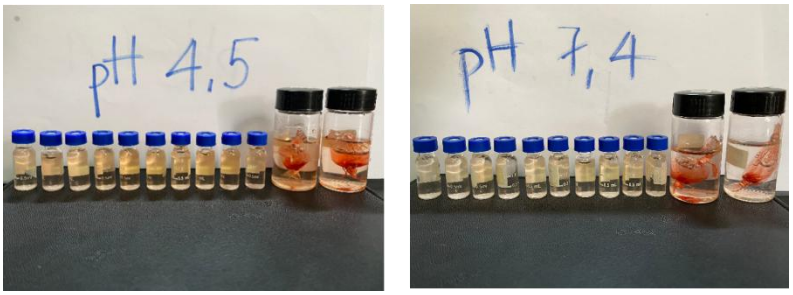


Figure 5: DOX release process of DOX@PNS-CS system at pH 4.5 and pH 7.4

2.6 Characterization of samples

The FTIR spectra of the materials were recorded using an FTIR 6300 (Jasco). The sample's morphology was examined using a HITACHI Regulus 8100 scanning electron microscope. XRD (PAN Empyrean) was used to evaluate the sizes and structures of nanosilica and nanosilica collagen. The NOVA 4200e

(Quantachrome instrument) was used to assess the surface area and pore size. furnace made by Thermo Scientific.

3 RESULTS AND DISCUSTION

3.1 EDX analysis results of elemental content in coconut coir

The EDX results, as shown in Figure 6 and Table 1, indicate that the coconut fiber ash sample has the highest mass percentages of O and Si, at 53.51% and 31.78% respectively, proving that silica (SiO_2) is the main component in the sample. Additionally, Al, Na, and K appear in lower concentrations, while C and S are present in negligible amounts.

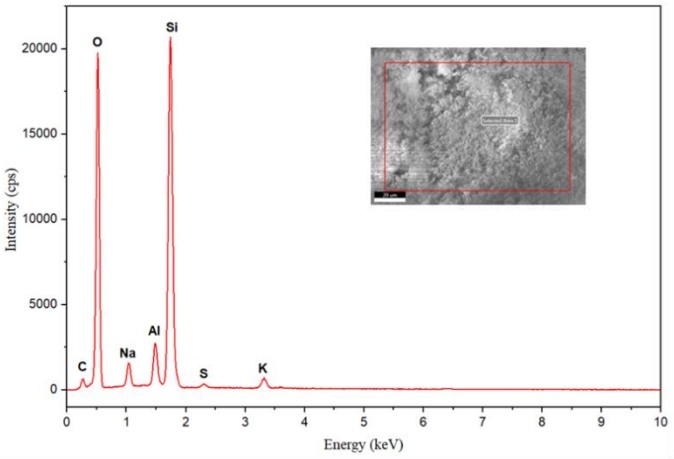


Figure 6: EDX spectrum of elemental composition in coconut coir ash

Table 1: Percentage of elements in coconut coir ash.

Elements	Percentage by weight (%)
O	53.51
K	1.84
C	3.98
Si	31.78
S	0.49
Al	4.33
Na	4.07
Total	100

3.2 Fourier Transform Infrared (FTIR)

The results of the Fourier transform infrared spectra in Figure 7 demonstrate that:
The stretching vibration of the OH group, nano silica has an absorption band in the range of 3398.92 cm^{-1} in FTIR spectra of PNS. The presence of asymmetric Si-O-Si is indicated by the broad and strong peak at 1057.76 cm^{-1} [6-8].
The FTIR measurement results in spectra of PNS-CS demonstrate that a prominent peak at 1603.52 cm^{-1} is characteristic of imine when nano silica is modified by chitosan mixture. The C=N bond shows a strong absorption band in the region of 1600-1690 cm^{-1} [9-11].
The C-H stretch on 3-glycidoxypropyltrimethoxysilane (GPTMS) was shown by peaks at 2900 and 2800 cm^{-1} [12].
The results of Fourier transform infrared spectroscopy demonstrated the successful modification of nano silica with chitosan biopolymer and the synthesis of nano silica materials.

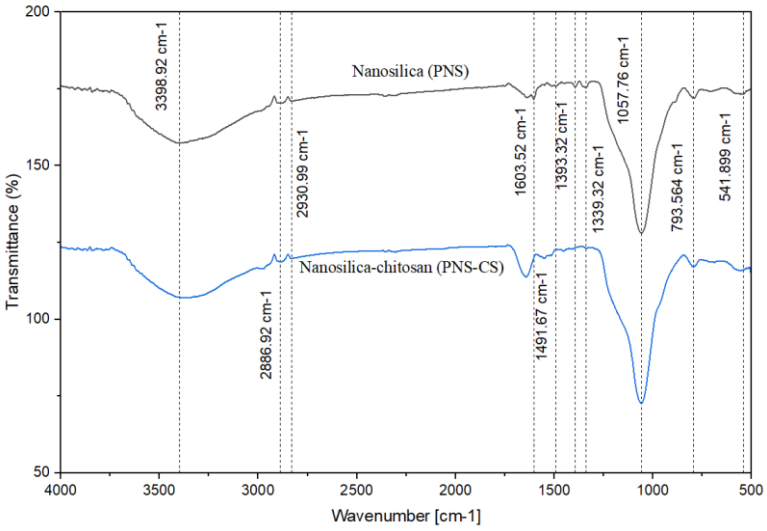


Figure 7: FTIR spectrum of nano silica (PNS) and nano silica-chitosan (PNS-CS)

3.3 Particle size and morphology properties

The results of SEM (scanning electron microscopy), we can determine the size and morphology of nano silica particles and nano silica after modification by chitosan (Fig. 8). Nano silica particles are spherical in shape, with an average size of 53.75 ± 16.44 nm. After modification, the resulting nano silica chitosan is also spherical in shape and has a slightly larger average size of 63.32 ± 16.73 nm.

To effectively deliver drugs into the veins, the size of drug-carrying particles must be between 20 and 200 nm. This size range will enhance permeability and retention (EPR). The EPR effect is a phenomenon in which tumor blood vessels have higher permeability than normal blood vessels [13, 14]. Through kinetic studies, it has been shown that particles with a size of about 20 nm will be excreted through the kidneys faster than particles with a size of 100 nm [15, 16].

From the above studies, it can be seen that the ideal drug-carrying nanoparticle is between 30 and 80 nm so that the particle can carry the drug to maintain circulation in the blood to the right tumor, release the drug and then be excreted from the body. Therefore, the resulting nano silica chitosan particles have met the requirements of safe size, can be an effective drug delivery system and be excreted from the body without affecting the patient's health.

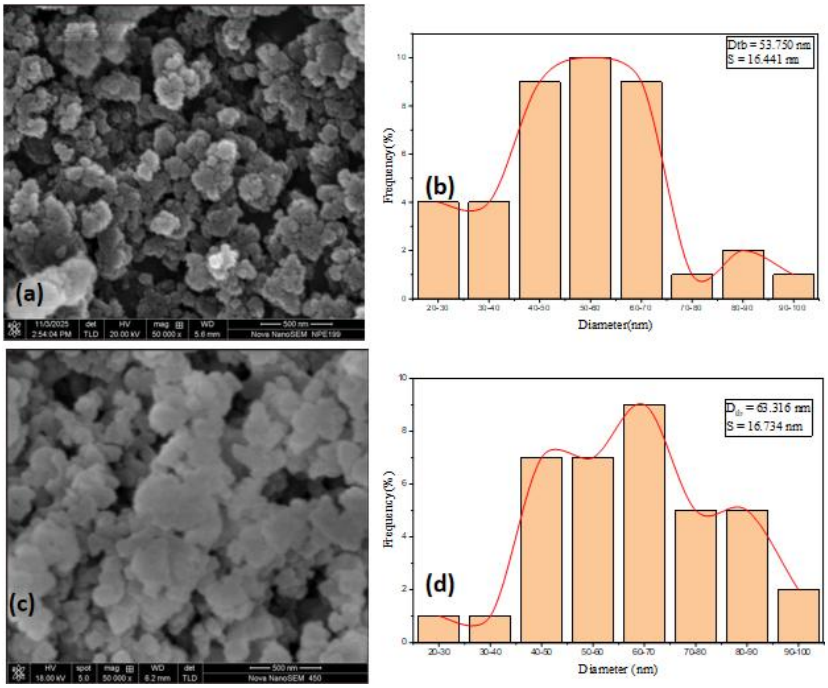


Figure 8: SEM images and particle size graph of PNS (a, b) and PNS-CS (c, d)

3.4 X-ray diffraction pattern

The calcination temperature plays a critical role in determining the structural evolution of biomass-derived silica materials. At temperatures below 500°C, carbonaceous residues are predominantly formed. In the temperature range of 500–800°C, amorphous nano silica is generated, whereas further increasing the calcination temperature to 800–1000°C results in the formation of crystalline silica phases [17, 18]. Among these, amorphous nano silica is considered more suitable for biomedical applications, particularly drug delivery systems, due to its favorable biocompatibility and safety profile [19, 20].

As shown in Figure 9, the X-ray diffraction (XRD) patterns of nano silica samples obtained from coconut coir ash calcined at 500°C and 600°C exhibit a single broad diffraction peak centered at approximately $2\theta = 22.79°$, which is characteristic of SiO_2, indicates the successful synthesis of high purity nano silica. Furthermore, the broad diffraction halo confirms that the synthesized silica possesses an amorphous structure rather than a crystalline phase [21, 22].

Pure chitosan exhibits a semicrystalline structure, whereas the incorporation of amorphous nano silica significantly alters its structural organization. The XRD pattern of pure nano silica (PNS) is characterized by a broad diffraction peak, consistent with its amorphous nature (Figure 9). Similarly, the XRD pattern of the chitosan-coated nano silica (PNS-CS) retains the broad diffraction feature, indicating that the composite remains predominantly amorphous. However, the diffraction peak of PNS-CS is slightly sharper than that of PNS, suggesting the successful interaction and incorporation of chitosan onto the nano silica surface while preserving the overall amorphous structure of the composite [23].

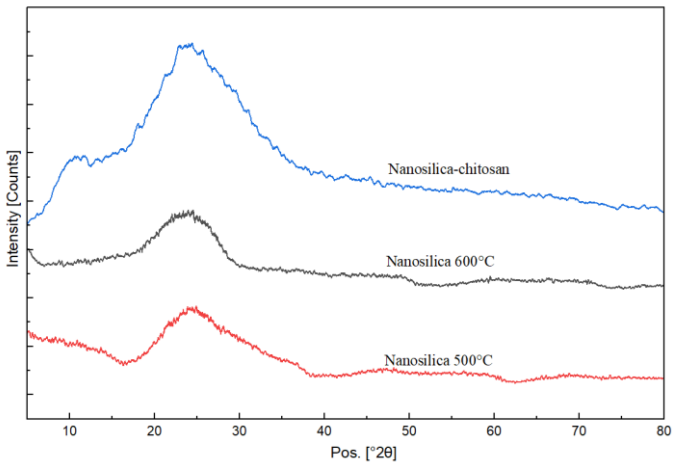


Figure 9: X-ray diffraction (XRD) images of nanosilica before and after chitosan modification.

3.5 N_2 adsorption-desorption isotherms (BET)

The N_2 adsorption–desorption isotherms (BET) shown in Figure 10 confirm the porous nature of the nano silica derived from coconut coir (600^o C). The BET analysis yielded a specific surface area of **276.152 m²/g**, a pore volume of **0.604 cm³/g**, and an average pore diameter of **10.066 Å** from the adsorption branch. The corresponding values obtained from the desorption branch were **322.330 m²/g**, **0.616 cm³/g**, and **11.632 Å**, respectively.

The high specific surface area and well-developed pore structure provide abundant adsorption sites for drug molecules, thereby enhancing the drug-loading capacity of the nano silica. Furthermore, the mesoporous architecture facilitates the diffusion of encapsulated doxorubicin, enabling sustained and controlled drug release. These findings demonstrate that the synthesized nano silica is a promising carrier for doxorubicin delivery, consistent with previous reports [17].

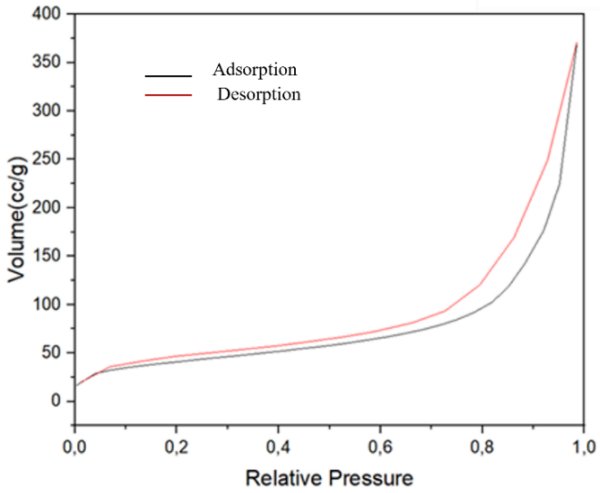


Figure 10: N_2 adsorption-desorption isotherms (BET)

3.6 Loading of Doxorubicin

Determining the amount of drug that has not been carried, we can easily analyze the drug loading efficiency and drug capacity of the particle. After measuring the amount of excess drug that has not been carried by UV-VIS, we have the following results in table 2. The findings demonstrated that the drug loading efficiency and drug capacity of the chitosan-modified nano silica system containing DOX were both comparatively greater than those of other modified [18-21].

Table 2: Comparison of DLE and DLC data of PNS- CS and PNS

Sample	DLE (%)	DLC (%)
DOX@PNS-CS	71.75 ± 1.89	12.55 ± 0.27
PNS loading DOX	23.01 ± 2.16	2.09 ± 0.32

3.7 In Vitro Doxorubicin Release

As shown in Figure 11, the chitosan-modified porous silica nanosystem exhibited a pronounced pH-dependent DOX release behavior. At pH 7.4, which approximates the physiological pH of healthy tissues, only 30.22% of the loaded DOX was released. In contrast, at pH 4.5, corresponding to the acidic environment typically associated with tumor tissues and intracellular lysosomes, the cumulative DOX release reached 70.65%. These results indicate that the PNS-CS drug delivery system effectively suppresses premature drug release under physiological conditions while promoting drug release in acidic environments, suggesting its potential to reduce off-target toxicity toward healthy tissues and enhance selective drug delivery to cancer cells.

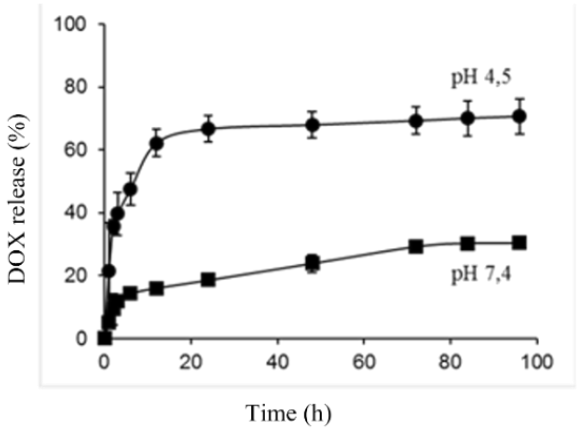


Figure 11: Survey of DOX release

3.8 Half maximal inhibitory concentration (IC50) of the nanosilica modified by chitosan (CS) material and DOX loading

The 50% inhibitory concentration (IC50) of DOX and the DOX-carrying CS denaturation system (DOX@PNS-CS) against the human breast cancer cell line MCF-7 and the healthy cell fibroblast were investigated. The DOX-carrying PNS-CS drug delivery system is far less hazardous than DOX alone, according to Table 3's findings.

Table 3: Inhibitory concentration (IC 50) of DOX and the nano silica denatured CS loading DOX (DOX@PNS-CS)

Sample	Cell line	IC 50 (µg/mL)
DOX	MCF-7	0.062 ± 0.001
DOX@PNS-CS		2.59 ± 0.29
DOX	Fibroblast	1.17± 0.04
DOX@PNS-CS		10.08 ± 1.04

Additionally, the DOX@PNS-CS drug delivery system is specific to cancer cells and safe for healthy cells, as evidenced by the IC50 value of the chitosan-modified nano silica material loading DOX, which demonstrated a strong cytotoxic effect on MCF-7 cells and a weaker effect on fibroblasts (healthy normal cells)[22, 23]. Figure 12 &13.

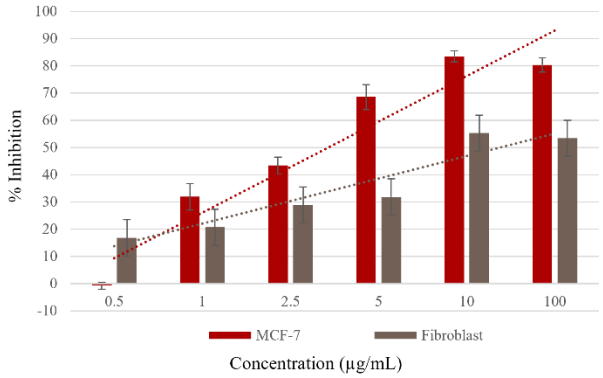


Figure 12: Cytotoxicity of DOX, and DOX@PNS-CS on MCF-7 and Fibrobalst

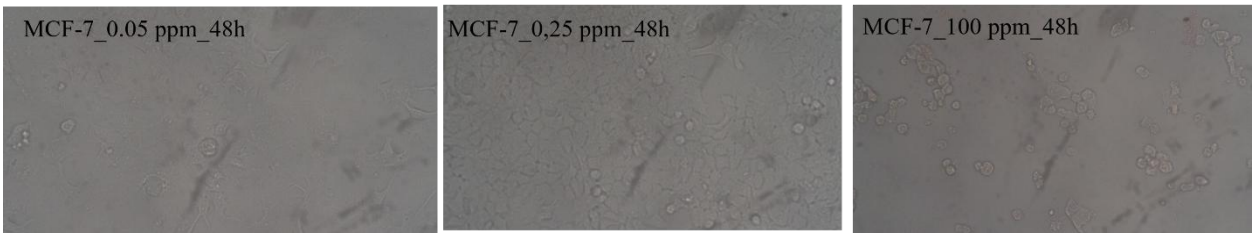


Figure 13: MCF7-cell line reponse DOX@PNS-CS

4 CONCLUSIONS

Porous nano silica (PNS) was successfully synthesized from coconut coir, an abundant agricultural waste, demonstrating a sustainable alternative to conventional silica precursors. The synthesized nanoparticles exhibited a spherical morphology with an average particle size of 53.75 ± 16.44 nm and a high specific surface area of approximately 322.33 m^2/g. Surface functionalization with chitosan produced PNS-CS nanoparticles with an average diameter of 63.32 ± 16.73 nm. X-ray diffraction analysis confirmed the amorphous nature of the synthesized nano silica, indicating its suitability for biomedical and pharmaceutical applications.

Drug loading and release studies demonstrated that chitosan functionalization introduced amino groups capable of forming pH-responsive imine (Schiff base) linkages with doxorubicin (DOX). These acid-labile bonds remained stable under physiological conditions while undergoing hydrolysis in acidic environments, enabling controlled and selective drug release under tumor-mimicking conditions. The DOX-loaded chitosan-functionalized nano silica (DOX@PNS-CS) exhibited enhanced anticancer activity against MCF-7 breast cancer cells, while showing lower cytotoxicity toward normal fibroblasts compared with free DOX. These findings indicate that chitosan-functionalized porous nano silica can improve the therapeutic selectivity of DOX and reduce its adverse effects on healthy cells.

Overall, this study demonstrates the feasibility of developing a pH-responsive drug delivery platform from coconut coir without the use of tetraethyl orthosilicate (TEOS), providing a sustainable and environmentally friendly strategy for nano silica production. The valorization of agricultural waste into high-value nanomaterials not only offers a cost-effective approach for targeted drug delivery but also contributes to waste management and supports the principles of sustainable development and the United Nations Sustainable Development Goals (SDGs).

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